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DATE MAILED: 03/07/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 11/14/94 ☐ This action is made fina

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-34 are pending in the application

Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-34 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Claims 1, 2, 8, 10, 17, 21-26 and 29 have been amended.
Claim 34 has been added.
Claims 1-34 are pending.

REJECTIONS WHICH STILL REMAIN AND RESPONSE TO APPLICANT'S ARGUMENTS

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title should be addressed to the specificity which relies on a common epitope between E-selectin and L-selectin.

16. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 8.

Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

Applicant will submit formal drawings when allowable subject matter is indicated.

17. The previous rejection of claims 3-5, 10-18, 21-23 and 26-33 under 35 U.S.C. § 101 is withdrawn.

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

A) Applicant has not disclosed how to use E-/L-selectin-specific antibodies therapeutically in humans. There is insufficient information or nexus with respect to the in vivo operability of E-/L-selectin- specific antibodies to use applicant's invention.

Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification. Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986).

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences. Concerning selectin-mediated therapy, Harlan states that "whether you go humanized antibody, peptide soluble receptor, or saccharide , it's still a long way to a product" (1449, #4; Edgington, Biotechnology, 1992, page 386, column 3, paragraph 4). Furthermore, the therapeutic indices of drugs or biopharmaceuticals are often species- and model-dependent.

Applicant has not provided sufficient evidence a priori that establishes the efficacy of the claimed invention for the treatment of human inflammatory diseases. Although the EL-246 antibody was shown to inhibit leukocyte binding in vitro and in vivo in an animal model, no clear nexus has appeared in the application to predict E-/L-selectin-specific immunotherapy of human diseases. Therefore it does not appear that the asserted operability of the claimed method and compositions for treating human inflammatory diseases would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be

required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

Applicant's arguments have been fully considered but are not found convincing. Applicant argues that those skilled in the art would accept the in vivo, ex vivo and animal models as predictive of efficacy in humans in the treatment of inflammatory diseases. Applicant argues that it would not be "undue" experimentation to ascertain the claimed antibody specificities for diagnosis and therapy. Applicant in conjunction with the Steinberg declaration show that the EL-246 antibody had an in vivo effect on a lung ischemia/reperfusion animal model. Applicant also refers to the positive outlook for selectin-mediated therapy provided in certain sections of the Edgington reference, however there is no clear evidence that such selectin-based therapeutics are working in humans or that the acknowledged limitations of such selectin-based therapy have been overcomed.

The examiner maintains the position that the efficacious treatment of targeted diseases is not predictive from the experimental evidence for the reasons of record. it is noted that the instant exemplification of EL-246 antibody treatment in a lung reperfusion injury model was based upon the administration of antibody prior to reperfusion (Steinberg et al., J. Heart Lung Transplant, 1994; Exhibit 3, filed 1/29/94; see Abstract). Although the animal models validate concepts based on studies of human disease, such studies are limited usually to the "acute" as opposed to "chronic" nature of diseases. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly over time, with natural periods of disease exacerbation and remission. In the instant application, antibody treatment occurred before the stimulus of the inflammatory response, therefore it is not clear that antibody treatment would be effective under normal clinical conditions.

Concerning the use of EL-246 antibody-based therapy, Bargatze et al. (J. Immunol., 1994) disclose that human lymphocytes, although showing tissue-specific lymphoid localization and apparent EL-246 blocking, accumulated in inconsistent and small numbers, making it not possible to generate statistically significant data (Discussion, column 2, page 5823, paragraph 2). These authors further state that the most important test of the effectiveness of EL-246 in vivo will come from studies in which the antibody is injected into animals and the effect on either lymphocyte recirculation or inflammation is evaluated (page 5823, column 2, paragraph 1). Although Steinberg et al., J. Heart Lung Transplant, 1994 is cited as supportive preliminary experiments, the authors and others clearly indicate limitations to clinical practice of selectin-

based therapy (Discussion, particularly the last paragraph and Scientific Sessions Discussion).

Concerning antibody-based therapy, Mountain et al. teach that most antibody-based therapies are very unlikely to achieve success with a single dose (Biotechnology and Genetic Engineering Reviews, 10: page 11, paragraph 1, first sentence, 1993). Similarly, the success of multiple dosing as a therapeutic regimen would not be expected to work. Murine antibodies are limited to one or perhaps two doses and the administration of further doses leads to accelerated clearance and in many cases to complete abrogation of efficacy (Mountain et al., pages 10-11, overlapping paragraph). In a brief review of adhesion therapy, Shaffer relays similar concerns about adhesion molecule-specific monoclonal antibodies, which are promising but involve toxicities and do not seem to have a lasting effect upon repeated use (Biotechnology Newswatch, 1993).

Applicant cites the use of OKT3 to support the use of antibody therapy. Waldmann clearly states that despite the wide ranging interest in monoclonal antibody therapy, the magic bullet of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved to be elusive (Science, 1991; page 1657, paragraph 3). This reference discloses that only one monoclonal antibody, OKT3, has been licensed for clinical use, however it is acknowledged that this number may be more than just one as of February, 1995. Jolliffe discloses that while OKT3 is effective for renal allograft rejection, OKT3 therapy for autoimmune diseases such as diabetes, multiple sclerosis and systemic lupus erythematosus has not been possible (Intern. Rev. Immunol., 1993). Therefore, even the successful use of OKT3 is limited to a particular therapeutic modality and is not broadly applied to any clinical circumstance where T cells would be targeted based upon in vitro and animal models.

Therefore, applicant's allegations concerning the validity of the examiner's position on the limitations of antibody therapy are not found convincing in light of clear teachings and experiences of the skilled artisan, as indicated above. In the absence of clear and convincing evidence commensurate in scope with the allegations and claims, applicant has not provided sufficient information or nexus a priori that establishes the efficacy of the claimed invention for the treatment of human inflammatory diseases.

The Steinberg declaration under 37 C.F.R. § 1.132 filed 11/29/94 is insufficient to overcome the rejection of claims 3-5, 10-18 and 26-33 based upon 35 U.S.C. § 112, first paragraph as set forth in the last Office action because of the reasons cited above.

B) It is unclear from the specification whether any common epitope, as recited in independent claim 1, found on E-selectin and L-selectin can serve as a diagnostic or therapeutic agent as the disclosed utility of the instant application. Applicant has exemplified only the common epitope between E-/L-selectins defined by the EL-246-specific antibody. There is no evidence relating to another common epitope between E-/L-selectins to enable the diagnostic and therapeutic utilities embraced by the instant invention. The disclosure is not enabled for any common antigenic determinant found on E-selectin and L-selectin, all of which are embraced by the claims. The specification has not provided sufficient direction or guidance to one of skill in the art to properly select a E-/L-selectin common epitope other than that defined by the EL-246 antibody which may provide diagnostic or therapeutic operability. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed specificity of common antigenic determinants found on E-/L-selectins using the teaching of the specification alone.

Applicant's arguments have been fully considered but are not found convincing. Applicant argues that the instant specification teaches how to make and screen for the antibodies of the claimed invention. However, applicant has not provided evidence of an epitope that is common to both E- and L-selectin or a common E-/L-selectin (or one restricted to the SCR) that is powerful inhibitor of multiple cell-cell interactions other than the epitope that is recognized by the EL-246 antibody. In a current publication on the E-/L-selectin common epitopes, Bargatze et al. discloses that only the EL-246 antibody appears to recognize an epitope common to both human E-/L-selectin which requires some portion of the SCR domain and can block cell-cell interactions mediated by E- or L-selectin (see Introduction, particularly page 5815, column 1, paragraph 1). In the absence of clear and convincing evidence commensurate in scope with the allegations and claims, applicant has not provided sufficient information or evidence a priori that establishes the appearance of an epitope common to both human E-/L-selectin other than that recognize by the EL-246 antibody.

Applicant should limit claims to the common E-/L-specific antigenic determinant defined by the EL-246 antibody.

C) The Jutila declaration under 37 C.F.R. § 1.132 filed 11/29/94 is sufficient to overcome the previous rejection of claims 1-33 based upon 35 U.S.C. § 112, first paragraph as set forth in the last Office action concerning the deposit of biological materials with respect to the EL-246 hybridoma.

21. Claims 1-6 and 8-34 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see sections 19-20).

22. The previous rejection of claims 10-17 and 26-29 under 35 U.S.C. § 112, first and second paragraphs, has been withdrawn in response to applicant's amended claims.

23. Claims 30-31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30-31 are indefinite in the recitation "endothelial cell layer" because "endothelial cells" is the more appropriate term.

Applicant's arguments have been fully considered but are not found convincing. Applicant points out certain sections of the specification to support this phrase. However, the examiner maintains that the phrase "endothelial cell layer" both recited in the specification and understood by the ordinary artisan would refer to an in vitro endothelial cell layer. The claims are drawn to in vivo therapeutic methods. Endothelium is the term used for the lining of vascular tissue. Again, applicant is invited to amend this phrase to endothelial cells or endothelium.

The amendments must be supported by the specification so as not to add any new matter.

It is noted that the other previous rejections under 35 U.S.C. § 112, second paragraph, have been withdrawn in response to the amended claims.

24. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies

as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25. The Jutila declaration filed on 11/29/94 under 37 C.F.R. § 1.131 is sufficient to overcome the previous rejection of claims 1-8 and 19-25 under 35 U.S.C. § 102(f). Applicant should make note that this declaration actually filed as a 37 C.F.R. § 1.131 declaration has been received as a 37 C.F.R. § 1.132 declaration and not a C.F.R. § 1.131 declaration.

26. The previous rejection of claims 1, 6, 18, 19, 21-25 under 35 U.S.C. § 102(b) as anticipated by Kishimoto et al. (1449, #38; PNAS, 1990, see entire document) as evidenced by Jutila et al. (1449, #40; J. Exp. Med., 1992) has been withdrawn in response to applicant's arguments.

27. Claims 1-34 are rejected under 35 U.S.C. § 103 as being unpatentable over Kishimoto et al. (1449, #38; PNAS, 1990) in view of Lasky et al. (1449; U.S. Patent No. 5,098,833), Bevilacqua et al. (1449; U.S. Patent No. 5,081034) and Watson et al. (1449, #23; Nature, 1991). Claims 1-34 are drawn to antibodies that recognize a common E-/L-selectin epitope and their use in diagnosis and therapy.

Kishimoto et al. teach the derivation of a number of L-selectin-specific antibodies including the DREG-56 antibody (see entire document). Kishimoto et al. teach the ability of the DREG-56 antibody to inhibit lymphocyte-endothelial binding in vitro. Kishimoto et al. also compare these observations with the ability of other L-selectin-specific antibodies to inhibit neutrophils and monocytes in addition to lymphocytes, which are useful for treating inflammation in vivo. Kishimoto et al. does not teachings making an antibody that binds a common E-/L-selectin epitope per se.

Lasky et al. teach the cloning of L-selectin and its use in the diagnosis and treatment of inflammatory diseases (see entire document). Similarly, Bevilacqua et al. teach the cloning E-selectin and its use in the diagnosis and treatment of inflammatory diseases. As disclosed in the specification, the prior art is replete of examples of L-selectin and E-selectin antibodies which inhibit various models of inflammatory diseases (see pages 1-10 of the specification). Watson et al. teach the use of L-selectin-specific molecules as therapeutic agents to inhibit viral infection or immune function (see entire document). Furthermore, Watson et al. teach that combinations of adhesion

molecules may be required to inhibit acute or chronic inflammatory responses (see page 166, column 2, paragraph 3). Here, Watson et al. corresponds the inhibitory effects of the L-selectin chimeric protein and E-selectin expression. Watson teaches that the rational design of anti-inflammatory regents should be based on competitive blocking of leukocyte-endothelial cell interactions.

Applicant has characterized the property of the EL-246 antibody as being directed towards a common E-/L-selectin epitope. Such specificity was already selected for by routine screening of L-selectin-specific antibodies that inhibited leukocyte-endothelial interactions and their use as diagnostic and therapeutic agents for human inflammatory diseases. The claimed limitations of antibodies specific for (common) E-/L-selectin epitopes or short consensus regions would have been met by the selection process disclosed in the prior art. The claimed limitations of inhibiting adhesion, leukocyte rolling, tissue damage, and inflammation would have been met by the selection for treating inflammatory diseases, as disclosed in the prior art.

Applicant is reminded that in submitting evidence asserted to establish differences and/or unobvious results sufficient to dissipate a prima facie case of obviousness, there is a burden on the patent applicant to establish not only that the differences in results achieved are in fact "unexpected and unobvious" but also to establish that the differences are of practical significance. See 27 USPQ2d Ex parte C (see page 1497, column 1, paragraph 4). It is not clear that a patentable distinction can be made upon differences in binding L-selectin from different species. The critical element remains in the selection for E-/L-selectin-specific antibodies to inhibit inflammatory processes in humans.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of L-selectin-specific antibodies as therapeutic and diagnostic reagents in treating human inflammatory diseases. The derivation of those antibodies which bind a common E-/L-selectin would have been a result of selecting for these properties,as evidenced by the DREG-56 antibody. Futhermore, the ordinary artisan would have coordinated addressing multiple adhesion molecules in the rational design of anti-inflammatory reagents including the relationship of E-selectin and L-selectin in leukocyte-endothelial interactions. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references,

especially in the absence of evidence to the contrary.

Applicant's arguments have been fully considered but are not found convincing. Applicant argues essentially ~~are directed to~~ the lack of recognition of a common epitope between E-/L-selectins in the prior art. Applicant has provided sufficient evidence that the DREG-56 antibody and the instant EL-246 antibody bind different epitopes. However, the combined teachings clearly were drawn to the selection of those antibodies that inhibited leukocyte-endothelial interactions for diagnostic and therapeutic purposes in addition to characterizing the role of selectins in such cellular interactions. The immunogens and the antibody screening procedures of the cited references are the same as the instant invention. It is not necessary that the prior art was screening for or recognized a common epitope between E-/L-selectin. The prior art clearly were screening for powerful inhibitors of E-/L-selectin-mediated cellular interactions. Such screening procedures would have resulted in antibodies that recognized common E-/L-selectin epitopes. Upon standard characterization of the epitope specificity of such inhibitory antibodies, the ordinary artisan would have determined that certain E- or L-selectin specific inhibitory antibodies would have bound a common E-/L-selectin epitope. Applicant's arguments are not found persuasive and the rejection is maintained.

28. No claim is allowed.

29. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

30. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
March 1, 1995

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180

3/2/95